

# C1 (Esterase) Inhibitor (BERINERT<sup>®</sup>, CINRYZE<sup>™</sup>, RUCONEST<sup>®</sup>), Ecallantide (KALBITOR<sup>®</sup>), Icatibant (FIRAZYR<sup>®</sup>) for Hereditary Angioedema Criteria for Use June 2015

**VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

*The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE INCLUSION AND EXCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL LEVEL ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.*

The Product Information should be consulted for detailed prescribing information. The VA National PBM-MAP-VPE Drug Monograph for C1 Esterase Inhibitor (BERINERT), C1 Inhibitor (CINRYZE), C1 Esterase Inhibitor (RUCONEST), ecallantide (KALBITOR), icatibant (FIRAZYR) and icatibant monograph addendum, are available at [www.pbm.va.gov](http://www.pbm.va.gov) or <https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx> for further information. Note: when recommendations for "C1 Inhibitor" appear in the document, this includes C1 Esterase Inhibitor (BERINERT), C1 Inhibitor (CINRYZE), and C1 Esterase Inhibitor (RUCONEST).

## **EXCLUSION CRITERIA (if ONE is checked, patient is not eligible)**

- ☐ History of life-threatening acute hypersensitivity or anaphylaxis to C1 inhibitor, ecallantide or icatibant
- ☐ Angioedema or abdominal pain not associated with C1 inhibitor deficiency [Refer to Issues for Consideration for angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema]

## **INCLUSION CRITERIA (must fulfill first TWO criteria AND ONE of the following Indications to be eligible)**

- ☐ **Restricted to Allergy/Immunology; Dermatology; or for use in Emergency Medicine/Urgent Care**
- ☐ **Diagnosis of Hereditary Angioedema (HAE)** (must fulfill at least ONE of the following)
  - ☐ Type I [low serum complement factor 4 (C4), low C1 inhibitor protein]
  - ☐ Type II (low C4, normal or increased C1 inhibitor protein, low C1 inhibitor function)
  - ☐ Positive family history HAE and symptoms consistent with HAE (e.g., recurrent angioedema without urticaria, recurrent unexplained abdominal pain/vomiting, laryngeal edema)
- AND ONE of the following Indications**
  - ☐ **Severe<sup>a</sup> Acute HAE (C1 Inhibitor, Ecallantide or Icatibant)** [e.g., respiratory symptoms or laryngeal involvement, severe abdominal attack (severe pain with nausea and vomiting), significant orofacial swelling]
  - ☐ **Long-Term Prophylaxis (C1 Inhibitor<sup>b</sup>) [Must fulfill the following to be eligible for long-term prophylaxis]**
    - ☐ Intolerance, contraindication to, or inefficacy (e.g.,  $\geq 2$  per month used as inclusion criteria in clinical trials) with at least one other treatment recommended for long-term prophylaxis HAE attacks<sup>c,d</sup>
  - ☐ **On-Demand (C1 Inhibitor or Icatibant)<sup>b</sup>**
    - ☐ Frequent (e.g.,  $> 1$  every 3 weeks used as inclusion criteria in observational study with C1 inhibitor;  $> 24$  symptomatic days per year or  $> 12$  severe attacks per year per consensus report) severe HAE attacks despite prophylaxis with, or not on prophylaxis due to intolerance or contraindication to, attenuated androgens<sup>c</sup> or antifibrinolytics<sup>c</sup>
  - ☐ **Short-Term Prophylaxis (C1 Inhibitor<sup>e</sup>) [Both must be fulfilled in order to be eligible for short-term prophylaxis]**
    - ☐ Major procedure or intubation
    - ☐ Intolerance, contraindication to, or inefficacy with previous trial of either attenuated androgens<sup>c</sup>; antifibrinolytics<sup>c</sup>; or fresh frozen plasma

<sup>a</sup>Treatment with C1 inhibitor, ecallantide or icatibant in patients presenting with moderate HAE attack symptoms should be determined on a case by case basis (e.g., patient may respond to supportive care, symptom management, increased doses of attenuated androgens or antifibrinolytics); fresh frozen plasma also a treatment option for acute HAE

<sup>b</sup>Extensive education must be provided with patient and/or caregiver demonstration of understanding, and ability and willingness to administer treatment

<sup>c</sup>VA National Formulary agents include: attenuated androgens (danazol); antifibrinolytics (aminocaproic acid, tranexamic acid inj; oral tranexamic acid available non-formulary)

<sup>d</sup>May be appropriate to consider On-Demand therapy with C1 inhibitor or icatibant prior to implementing Long-Term Prophylaxis with C1 inhibitor, as indicated

<sup>e</sup>Published case report available on use of icatibant in short-term prophylaxis

## **DOSING AND ADMINISTRATION**

Refer to Product Information

## **MONITORING**

- C1 Inhibitor, ecallantide [Boxed Warning]: Evaluate for signs or symptoms of anaphylaxis and other symptoms of hypersensitivity (hives, urticaria, chest tightness, wheezing, hypotension); there have been no reports of hypersensitivity or anaphylaxis with icatibant
- C1 Inhibitor: Evaluate for signs or symptoms of thrombosis (new onset swelling or pain in limbs or abdomen, new onset chest pain or shortness

of breath, loss of feeling or mobility, or altered speech or consciousness)

## ISSUES FOR CONSIDERATION

### • FDA Approved Indications

- C1 Inhibitor (BERINERT) is approved for treatment of acute abdominal, facial or laryngeal attacks of HAE in adults and adolescents
- C1 Inhibitor (CINRYZE) is approved for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE
- C1 Inhibitor (RUCONEST) is approved for treatment of acute attacks in adult and adolescent patients with hereditary angioedema
- Ecallantide is approved for the treatment of acute attacks of HAE in patients  $\geq 12$  years of age
- Icatibant is approved for the treatment of acute attacks of HAE in patients  $\geq 18$  years of age
- Treatment of acquired angioedema with C1 inhibitor, ecallantide or icatibant is off-label and should be adjudicated on a case by case basis.
- Treatment with C1 inhibitor, ecallantide or icatibant in patients with acute hereditary angioedema presenting to the emergency department/urgent care should be administered with a provider available for emergent airway intervention, if needed.
- ACEI-induced angioedema: One clinical trial demonstrated a significant improvement with icatibant compared to standard therapy (i.e., corticosteroid and antihistamine) in time to complete resolution of symptoms in patients presenting for emergency management of ACEI-induced angioedema. It should be noted that patients with acute New York Heart Association class III or IV heart failure were excluded from this trial; therefore, safety and efficacy in this patient population are unknown at this time. In addition, patients in this study appeared to present with more mild to moderate symptoms of angioedema. Several case reports are also available reporting a benefit with icatibant in ACEI-induced angioedema. Additional data are needed to determine the overall impact, safety, and cost-effectiveness of icatibant in the management of ACEI-induced angioedema. At present, due to the limited data and off-label use, the need for use of icatibant for ACEI-induced angioedema should be determined on a case by case basis, reserving treatment for patients presenting with more severe symptoms with risk for airway obstruction. [Refer to further discussion in the Icatibant Monograph Addendum at: [PBM Drug Monographs](#)]. Two published clinical trials evaluating the use of ecallantide compared to conventional therapy for ACEI-induced angioedema did not find a statistically significant difference in the percent improvement in patients receiving ecallantide. Although no clinical trials are available at this time, case reports are available that demonstrate the potential benefit of using a C1 inhibitor in the management of patients presenting with emergency treatment of ACEI-induced angioedema.
- Icatibant has not been adequately studied in patients with acute ischemia; use during acute coronary ischemia, unstable angina, or in the weeks after a stroke should only be undertaken if the benefit outweighs the potential risk.
- Patients being considered for self-administration either for On-Demand therapy (C1 inhibitor, icatibant) or Long-Term Prophylaxis (C1 inhibitor) should receive education on the disease, indications for treatment, documentation of symptoms, and proper preparation and administration and be able to demonstrate understanding, and the ability and willingness to administer treatment with the agent. Due to the potential for anaphylaxis, ecallantide should be administered by a healthcare professional with medical support available and is not appropriate for self-administration in On-Demand therapy or Long-Term Prophylaxis. Due to the potential for airway obstruction, patients should be instructed to seek immediate medical care at a healthcare facility after self-administration for an acute attack with laryngeal involvement.
- Plasma derived C1 inhibitor (BERINERT, CINRYZE) have the potential risk for transmitting infectious diseases including viruses and Creutzfeldt-Jakob disease. Screening and testing measures as well as manufacturing processes have been implemented to reduce this risk. If it is felt that an infection could possibly be the result of plasma derived C1 inhibitor administration, this should be reported by the provider to the manufacturer and to VA ADERS. The risk vs. benefit of treatment with plasma derived C1 inhibitor should also be discussed with the patient. The recombinant analogue of human C1 inhibitor (RUCONEST) is purified from the milk of transgenic rabbits to reduce the risk for human viral transmission. There is no concern for viral transmission with ecallantide as it is not derived from human plasma. Icatibant is a synthetic peptide so there is not the concern for viral transmission with this agent.
- C1 inhibitor (BERINERT or CINRYZE), ecallantide and icatibant are Pregnancy Category C; C1 inhibitor (RUCONEST) is Pregnancy Category B. For C1 inhibitor (BERINERT, CINRYZE, RUCONEST) or ecallantide, it is recommended to use in pregnancy only if clearly needed; for icatibant, the recommendation is to only use if the potential benefit justifies the potential risk to the fetus. Patients should be provided contraceptive counseling and education on potential risk vs. benefit of taking C1 inhibitor (BERINERT, CINRYZE, or RUCONEST), ecallantide or icatibant if they were to become pregnant.